REMARKS/ARGUMENTS

Claims 18-23, 25, and 66-72 are pending in the above-identified application. In view of the remarks set forth below, Applicants respectfully request reconsideration of all pending claims.

Rejections under 35 U.S.C. § 101

Claims 18-23 and 25 stand rejected under 35 U.S.C. § 101 as allegedly not supported by either a credible asserted utility or a well-established utility. Applicants traverse this rejection as set forth below.

First, to summarize the basis for the rejection as stated in the Office Action, the Examiner contends the following:

(1) that a fusion protein comprising a CTL-stimulating peptide and the recited pan-DR peptide "cannot be processed to separate the CTL peptide from the pan-DR binding peptide and separately present it to CTL in the context of HLA class I"; and

(2) that it is well-known that "MHC class I molecules do not express antigenic peptides obtained via the exogenous pathway, a function exclusive to MHC class II."[1]

It is noted that no evidence has been presented to support these assertions. For this reason, according to the MPEP, Applicants are not required to provide rebuttal evidence to support utility of the claimed invention.[2] For the sake, however, of expediting prosecution of this application, Applicants have attached Exhibits 1-4,[3] which collectively show (a) that processing and presentation of exogenous, MHC class I-restricted antigens to T lymphocytes was

[1] Office Action dated July 11, 2005, at p. 3
[2] *See* MPEP § 2164.07 (I)(B).
[3] Exhibit 1: Heath *et al.*, *Immunol. Rev.* 199:9-26, 2004 (also referred to herein as "Heath *et al.*");
Exhibit 2: Staerz *et al.*, *Nature* 329:449-451, 1987 (also referred to herein as "Staerz *et al.*")
Exhibit 3: Chen & Jondal, *Scand. J. Immunol.* 59:545-552, 2004 (also referred to herein as "Chen & Jondal").
Exhibit 4: Alexander et al., J. Immunol. 168:6189-6198, 2002 (also referred to herein as "Alexander *et al.*").

a phenomenon known in the art as of the effective filing date of the instant application; and (b) that linkage of a CTL-stimulating peptide to a T helper-stimulating peptide is, in fact, useful for stimulation of CTLs.

With regard to processing of exogenous antigen into MHC class I-binding peptides and subsequent presentation of such peptides to CTL, Heath *et al.* (Exhibit 1) describes the ability of certain cell types to "cross-present" MHC class I-restricted antigens from exogenous sources. As stated in Heath *et al.*, the "demarcation between endogenous and exogenous is not as strict" for some antigen-presenting cells, particularly dendritic cells, and "MHC class I-restricted presentation of both sources of antigen can occur."[4] This ability of exogenous antigen to be cross-presented to CTL was well-known as of the effective filing date of the instant application.[5] For example, Staerz *et al.* (Exhibit 2) describes one early study showing the induction of CTL specific for ovalbumin fragments by immunization with soluble protein. Staerz *et al.* state the following:

> As it is clear from our data that at least part of the activity induced by our immunization protocols is carried out by conventional CTL recognizing epitopes found on ovalbumin, there cannot be a complete separation of the two pathways of antigen presentation for MHC class I-restricted and MHC class II-restricted antigens. Our data indicate the existence of a mechanism allowing exogenous antigens to be presented in conjunction with MHC class I molecules in a similar way to antigens expressed within the cell.[6]

Staerz *et al.* go on to point to the existence of "specialized antigen-presenting cells" responsible for the observed activity.[7] As discussed by Heath *et al.* as well as Chen & Jondal (Exhibit 3), the antigen-presenting cells primarily responsible for such cross-presentation are, in fact, the "professional" APCs known as dendritic cells (DCs). Indeed, as stated by Chen & Jondal, while intracellular proteins are processed to form MHC class I-binding peptides, "***most***

[4] Exhibit 1 at p. 10 (first col., last paragraph, bridging to second col.).
[5] *See generally, e.g., id.*, citing pre-filing date references at, for example, p. 11, bridging to p. 12.
[6] Exhibit 2 at p. 451, first col. (emphasis provided).
[7] *Id.*

CTL responses are probably intitiated by the uptake of ***exogenous*** antigens into DC in a process called 'cross-priming.'"[8]

In view of the above, the asserted utility for the present invention, *inter alia*, to provide peptides for inducing or enhancing an immune response, is credible. The skilled artisan would reasonably accept that a peptide containing both an MHC I-restricted epitope and an MHC II-restricted epitope can be appropriately processed and presented to generate cytotoxic T lymphocyte (CTL) and helper T lymphocyte (HTL) immune responses. Indeed, as evidence that such a peptide does in fact induce both CTL and HTL responses, Applicants respectfully refer the Examiner to Alexander *et al.* (Exhibit 4). Alexander *et al.* describes the use of multideterminant peptides containing a pan DR epitope covalently linked to one or more CTL epitopes in priming *ex vivo* and *in vitro* recall $CD8^+$ and $CD4^+$ responses.[9] Significant responses were primed with as few as two epitopes (*i.e.*, the pan DR epitope covalently linked to one CTL epitope).[10]

Accordingly, because exogenously provided CTL-stimulating peptides can be appropriately processed and presented to CTL as set forth above, and because this function was recognized in the art as of the effective filing date, claims 18-23 and 25 are supported by a credible or well-established utility. Withdrawal of the present rejection is respectfully requested.

[8] Exhibit 3 at p.545, first col. (emphasis provided).
[9] *See* Exhibit 4.
[10] *See id.* at, *e.g.*, p. 6193, second col., first and second full paragraphs.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 18-23 and 25

Claims 18-23 and 25 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. In particular, on the basis of an alleged lack of utility for claims 18-23 and 25 as set forth in the Examiner's rejection under 35 U.S.C. § 101, the Examiner states that one skilled in the art would not know how to use the claimed invention.

Applicants traverse the instant rejection. For the reasons discussed in response the rejection under 35 U.S.C. § 101, claims 18-23 and 25 are supported by a credible or well-established utility. Accordingly, the skilled artisan would know how to used the invention as claimed. Withdrawal of the rejection is respectfully requested.

Claims 66-72

Claims 66-72 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. The Examiner states that, while the claims are enabled for "a nucleotide encoding a fusion protein comprising a pan-DR binding peptide and a T-helper epitope that is presentable by HLA-DR," the claims are not reasonably enabled for the full scope of the recited nucleotides "encoding a fusion protein comprising a pan-DR peptide and non-DR presentable T-helper epitope."[11] Applicants traverse this rejection as set forth below.

To briefly summarize the basis for the rejection as stated in the Office Action, the Examiner believes that, because the peptide of SEQ ID NO:22 is disclosed as binding only to HLA-DR haplotypes, the recited "T helper peptide," to which SEQ ID NO:22 is linked, must also be a peptide "specifically presentable by the HLA-DR class II molecule to which it is attached."[12] It appears to be the Examiner's belief that a non-HLA-DR class II peptide, linked to SEQ ID NO:22, would not be presentable to class II-restricted T cells due to the association of SEQ ID NO:22 with HLA-DR. It further appears to be the Examiner's position that, because of the alleged inability of non-HLA-DR peptides to be presented in the context of the present

[11] Office Action dated July 11, 2005, at p. 3, paragraph 4.

invention, the skilled artisan would not be able to determine whether a T helper peptide is "a peptide recognized by a T cell receptor unless that T helper peptide is normally presented by an HLA-DR class II molecule."[13]

Applicants initially note that, because this rejection is based on the contention that a skilled artisan would not know "how to use" the full scope of the recited fusion protein, the true thrust of this rejection is an alleged lack of utility under 35 U.S.C. § 101. As stated in the MPEP, "when a compound or composition is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of the claim is sufficient to preclude a rejection for nonenablement based on how to use."[14]

In this regard, the basis for the present rejection appears similar to that stated for the rejection under 35 U.S.C. § 101 of claims 18-23 and 25, reciting a fusion protein comprising SEQ ID NO:22 and at least one CTL-inducing peptide. To the extent that a fusion protein comprising SEQ ID NO:22 and a second T cell epitope can be appropriately processed to separate the second T cell epitope from SEQ ID NO:22, and subsequently presented by an MHC molecule, the fusion protein as claimed has an enabled use.

In the present case, the exogenous pathway for processing of MHC class II-restricted epitopes is well-established. Indeed, in view of the Examiner's stated reasons for rejection of claims 18-23 and 25 under 35 U.S.C. § 101, the Examiner already appears to accept that MHC class II peptides can be appropriately processed from an antigen when provided exogenously. Accordingly, one of skill in the art would readily accept that a fusion protein as recited in claim 66, comprising two MHC class II-restricted epitopes (*i.e.*, the pan DR-binding peptide of SEQ ID NO:22 and the "T helper peptide") would be useful for inducing or enhancing an immune response, since each peptide of the fusion could be processed and separately presented. In the particular case where the "T helper peptide" is a non-HLA-DR-presentable peptide, the peptide could be separated from SEQ ID NO:22 and presented in the context of a corresponding non-HLA-DR molecule to which it specifically binds.

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[12] *Id.* at p. 4.
[13] *Id.*
[14] MPEP § 2164.01(c) at 2100-187.

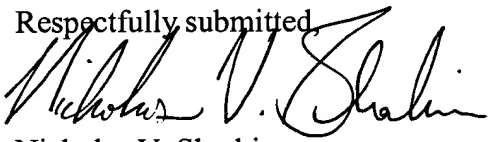
Therefore, in view of the knowledge in the art regarding processing and presentation of MHC class II-restricted peptides, as discussed above, there is insufficient basis for the present rejection of claims 66-72 under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,



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